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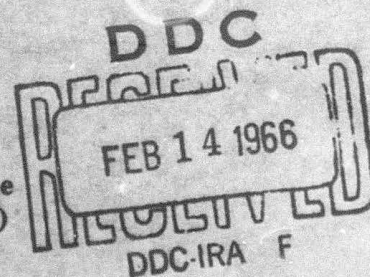
The Radiations of Space IV

GLENN V. DALRYMPLE, Captain, USAF, MC, et al.

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October 1965

USAF School of Aerospace Medicine
Aerospace Medical Division (AFSC)
Brooks Air Force Base, Texas



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SOME EFFECTS OF 400 MEV PROTONS ON PRIMATES

The Radiations of Space IV

GLENN V. DALRYMPLE, Captain, USAF, MC

IAN R. LINDSAY, Wing Commander, RAF, Exchange Officer

JOHN J. GHIDONI, Captain, USAF, MC

JOHN C. MITCHELL, B.S.

IRA LON MORGAN, Ph.D.*

***Texas Nuclear Corporation, Austin, Texas.**

FOREWORD

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The experiments reported herein were conducted according to the "Principles of Laboratory Animal Care" established by the National Society for Medical Research.

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This report has been reviewed and is approved.

Harold V. Ellingson
HAROLD V. ELLINGSON
Colonel, USAF, MC
Commander

ABSTRACT

Primates were given spaced doses of 400 Mev protons. From the mortality data an $LD_{50/30}$ of 585 ± 33 (S.E.) rads was calculated. Hematologic measurements, LDH and SGOT concentrations, ^{59}Fe ferrokinetics, and histopathologic findings indicate the effects produced by the protons are virtually identical to those produced by equivalent doses of 2 Mev x-rays. The only differences in response were clinical; relatively more intense gastrointestinal and hemorrhagic signs occurred after proton irradiation than after similar doses of the x-rays.

SOME EFFECTS OF 400 MEV PROTONS ON PRIMATES

The Radiations of Space IV

I. INTRODUCTION

In previous studies the biologic effects of 32, 55, and 138 Mev protons have been examined (1, 2, 3). At these energies the predominant mode of energy deposition results from direct ionization; nuclear processes which produce high LET-high RBE particles (recoil nuclei, evaporation nucleons, and others) provide less than 10% of the total rad dose (4).

In the experiments described in this communication, the biologic effects produced by 400 Mev protons are explored. This energy is of interest because it is about the highest energy represented by significant numbers of protons in the space proton spectrum (5). Since at 400 Mev some 25% of the total rad dose results from nuclear processes (4), the use of a monoenergetic source of these protons allows an evaluation of biologic effects occurring when the relative concentration of the high LET-high RBE particles equals or exceeds the maximum anticipated from irradiation with the space proton spectrum.

II. EXPERIMENTAL METHODS AND MATERIALS

One hundred twenty-three small primates (*Macaca mulatta*) were used. Of these, there were 57 males and 66 females. They had a mean weight of $3.7 \pm .6$ (S.D.) kg. The animal care practices used at the USAF School of Aerospace Medicine have already been described (6).

The University of Chicago Cyclotron Facility was used as a source of the protons. The details of the experimental arrangement, the beam characteristics, and the dosimetry have been previously documented (7, 8). In all, 9 groups of 3 to 17 animals were given spaced

single doses of protons ranging in size from 25 to 1,200 rads (table I). The protons were delivered at a dose rate of 16 rads/min.

From 7 of the dose groups (table I), selected animals were bled by femoral venipuncture before irradiation and at 1, 2, 4, 7, 15, 30, 60, and 90 days postexposure for hematologic studies and serum enzyme assays (6). Total white cell counts, white cell differentials, platelet counts, hemoglobin concentrations, microhematocrits, lactic dehydrogenase (LDH) concentrations, and glutamic oxalacetic transaminase (SGOT) concentrations were measured.

Five groups of 3 animals each were given doses of 25, 50, 100, 200, and 400 rads, respectively (tables I and IX). At least a month prior to irradiation, ^{59}Fe ferrokinetics were performed according to methods described by Lajtha (9); plasma disappearance half-times and 10-day RBC uptakes were measured. At 48 hours after exposure, the examinations were repeated.

A Van de Graaff accelerator was used for the 2 Mev x-irradiations. The experimental arrangement, the beam characteristics, and the dosimetry have already been described (6). A dose rate of 15 rads/min. was used. Five groups of 3 animals each received single doses of 25, 50, 100, 200, and 400 rads, respectively. Two sham-irradiated controls were also carried with this group. At least a month before exposure and at 48 hours postirradiation, ^{59}Fe ferrokinetics were performed.

During the first 60 postirradiation days, the animals were observed hourly for clinical changes and dead animals. They have been followed at about 8-hour intervals since the 60th day. All dead animals were necropsied and tissues processed according to methods already described (6).

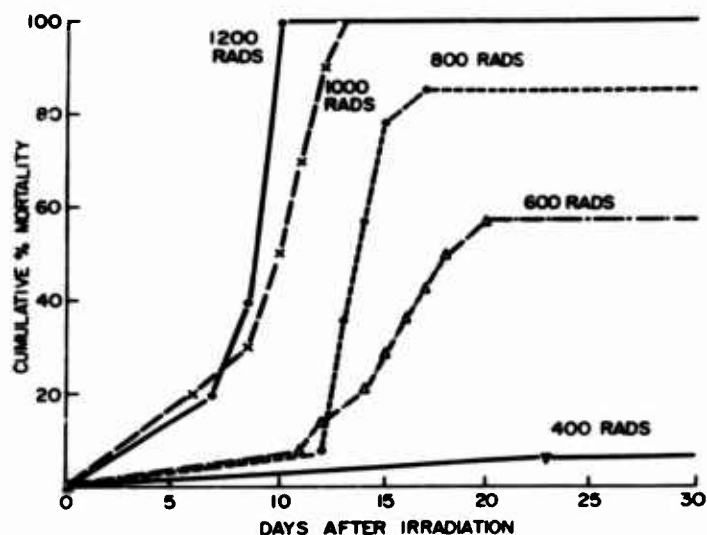


FIGURE 1

Cumulative mortality after irradiation. Since no deaths occurred after 200 rads and less, this was not plotted.

3d and 10th postirradiation days; mucous and bloody diarrhea were common. Lower doses (400 to 600 rads) caused proportionately less severe signs as compared with the higher doses. The gastrointestinal signs abated, however, in those animals which survived past the 10th day. This respite was only transitory, however, because evidence of hemorrhagic diatheses appeared on or about the 12th day. Extensive dermal petechiae and hemorrhages, gingival hematomas, and hemorrhages throughout the viscera were the most significant findings. Comparison of the clinical changes after 400 Mev proton irradiation with the findings from a previous study in which 2 Mev x-rays were used indicates a moderate increase in severity of both gastrointestinal disease and hemorrhage after equivalent doses of the protons (6).

The total white cell counts, the lymphocyte counts, the neutrophil counts, the platelet counts, the hemoglobin concentrations, and the hematocrits are summarized in tables II-VI, respectively. Both qualitatively and quantitatively, the changes of all of the measurements were similar to those previously observed in primates after orthovoltage and supervoltage electromagnetic radiations and after 138 Mev protons

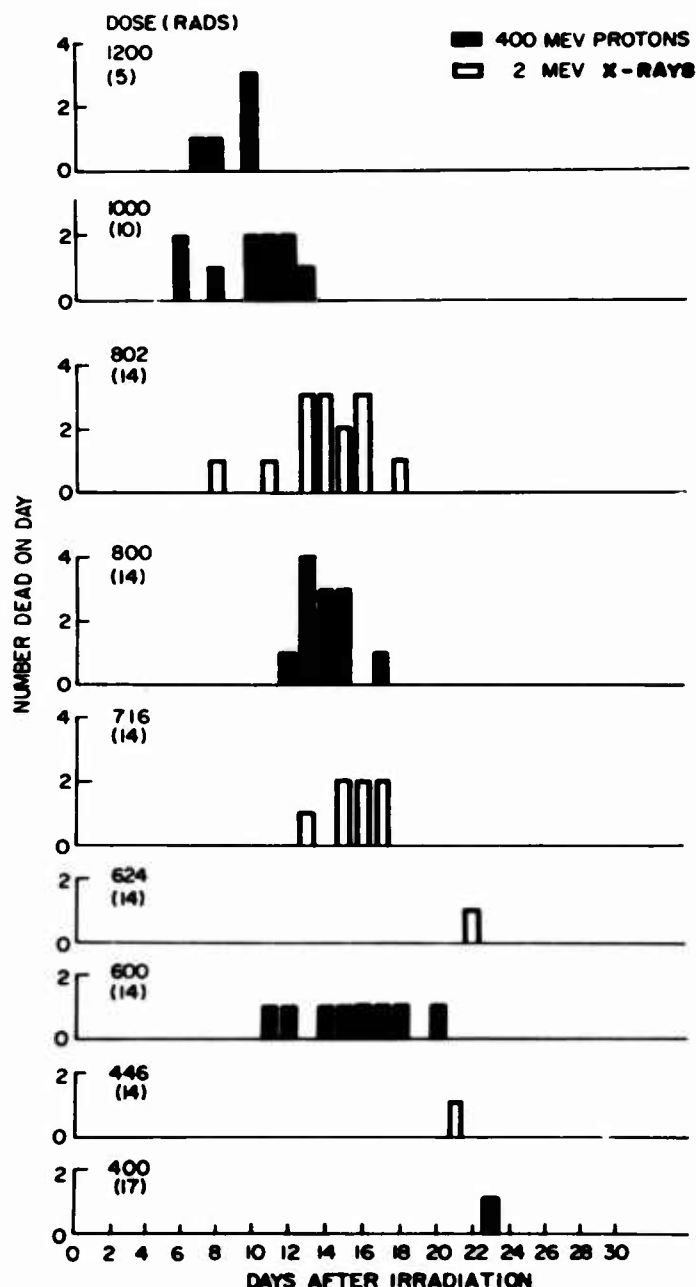


FIGURE 2

Daily mortality after irradiation with 400 Mev protons and 2 Mev x-rays.

(3, 6, 11, 13). During the first 2 postirradiation weeks, there occurred a progressive depression of the total white cell and lymphocyte counts—the latter, to a greater degree; a minimum was reached on day 15. The platelet counts remained at normal levels until the 15th

Since the histopathologic examination of the tissues taken at necropsy showed changes which were very similar to those found after 2 Mev x-ray and 138 Mev proton irradiation (3, 6), only a brief description of the findings will be given. A detailed analysis of the tissue changes after 400 Mev proton irradiation will be published separately. There were prominent changes throughout the large and small intestine; these changes included denudation of the mucosa and extensive microhemorrhages. While these findings were present in all dead animals, they were more severe in the higher dose groups (800 to 1,200 rads). All dead animals had aplasia of the bone marrow and severe hypoplasia of the lymph follicles of the spleen and lymph nodes. As was seen after 2 Mev x-irradiation, there were bacterial colonies scattered throughout the liver, lungs, kidneys, lymph nodes, and skin (6). Also, the lungs of several animals had the small abscesses without leukocytic infiltration as previously found in 2 Mev x-irradiated animals. When the tissue of animals which received equivalent doses of 2 Mev x-rays and 400 protons were compared, no significant differences were found.

IV. DISCUSSION

In an earlier study a large group of primates were irradiated with 2 Mev x-rays (6); these results will serve as an electromagnetic standard for estimating the relative biologic effectiveness (RBE) of the 400 Mev protons. As previously described, a most important consideration, in the estimation of RBE's by comparison of the $LD_{50/30}$, concerns parallelism of the probit regression curves (3, 10, 17). As Finney has stated, there are serious theoretic difficulties associated with estimating the relative potencies (RBE's in this case) of 2 or more treatments (radiations) when the probit regression curves are not parallel. A chi-square of 1.0185 (1 d.f.) for deviation from parallelism between the regression curves for 2 Mev x-rays and 400 Mev protons was calculated according to Finney's method (10). Since this value is not significant at the .05 level, the possibility of a significant departure from parallelism is rejected.

Because there is no reason to suspect deviation from parallelism, the RBE may be determined by the ratio of the $LD_{50/30}$'s. The $LD_{50/30}$ produced by 2 Mev x-rays was 670 ± 21 (S.E.) rads, and the $LD_{50/30}$ found after 400 Mev proton irradiation was 585 ± 33 (S.E.) rads; from these results, an RBE of $1.14 \pm .07$ (S.E.) was estimated (6).

Another important consideration is that of dose rate. Since many biologic effects produced by electromagnetic radiations are affected by the rate of delivery of the doses (14, 15, 16), this factor may play an important role in the present situation. Although the mortality after proton irradiation has not yet been shown to be dose-rate dependent, fragmentary evidence exists which suggests that such may be the case (17). To compensate for the possible influence of dose rate, the 2 Mev x-ray $LD_{50/30}$ was adjusted to the proton dose rate by a mathematical model derived by Bateman et al. (16). After this alteration had been made, an adjusted RBE of 1.09 was calculated. It is evident, therefore, that the 400 Mev proton-2 Mev x-ray RBE for mortality is essentially unity.

The prominent gastrointestinal signs after proton irradiation have been observed in both primates and rodents (3, 17, 18, 19). In the previous study in which 138 Mev protons were used, the gastrointestinal signs were somewhat more severe than in the present case. Since the 138 Mev protons were delivered at 57 rads/min. while the 400 Mev protons were given at 16 rads/min., part or all of this difference may be a consequence of the variation in dose rate. Comparison of the clinical findings after 2 Mev x-rays with both the 138 and 400 Mev proton experience, however, shows unequivocally that more severe signs were produced by the protons. Unfortunately, no explanation for this finding is available at present.

A similar circumstance exists about the severity of the postirradiation hemorrhagic disease. After both 138 and 400 Mev proton exposure, the degree of hemorrhage was considerably more extensive than after 2 Mev x-irradiation. Where small dermal petechiae

appeared after the x-rays, equivalent doses of the protons produced massive intradermal hemorrhages. Attempts to explain this phenomenon on physical grounds alone have been unsuccessful (3). There seems to be relatively little (if any) buildup of dose in the bone marrow cavities after the proton irradiation as compared to the x-rays.

A possible mechanism may be found in the clinical experience of physicians treating patients with chronic thrombocytopenia. In these cases a minimal infection or a transient bacteremia seems to trigger a hemorrhagic crisis (20-23). Since there appears to be considerably more gastrointestinal injury after the proton exposures, the injured intestinal epithelium could conceivably allow intermittent showers

of bacteria into the bloodstream and increase the severity of the thrombocytopenia. Since no blood samples were taken on days 8 to 14 or 16 to 29, the failure to find a sharply lowered platelet count is possible, especially if the hemorrhage episodes occurred as fulminant crisis and produced death in a matter of hours. Because the gastrointestinal signs after 2 Mev x-irradiation are considerably less severe than after proton exposure, it is possible that such bacteremias would be less likely to occur if the degree of intestinal injury was proportionately less severe. There are findings, however, which do not directly support the hypothesis just given. Although the histologic sections of the intestines after both protons and the x-rays show extensive changes, no real differences in response can be quantitated. Therefore, the possibility that the increased hemorrhage

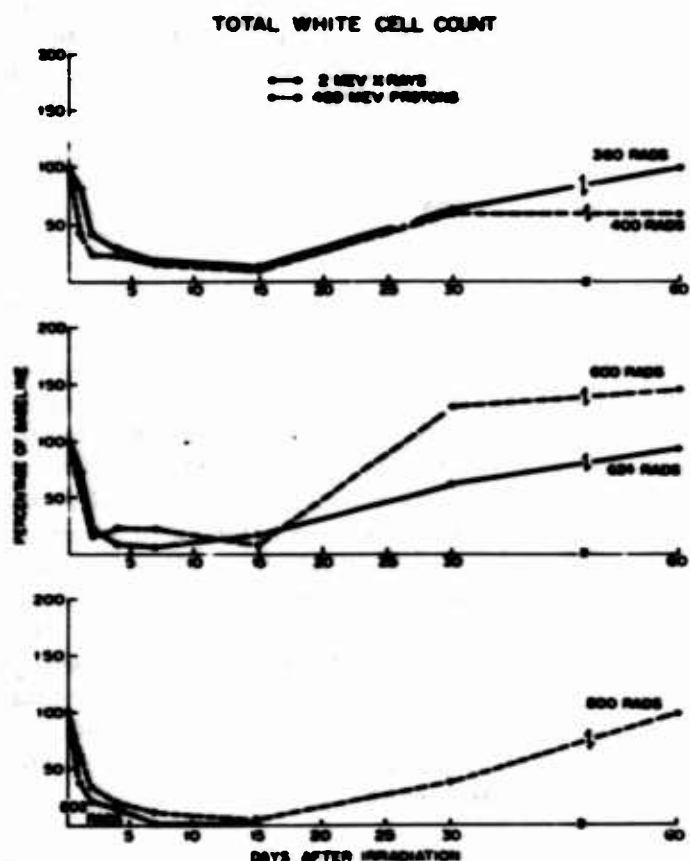


FIGURE 3

Total white cell counts after 400 Mev protons and 2 Mev x-rays. There were no survivors past 15 days after 802 rads of Mev x-rays.

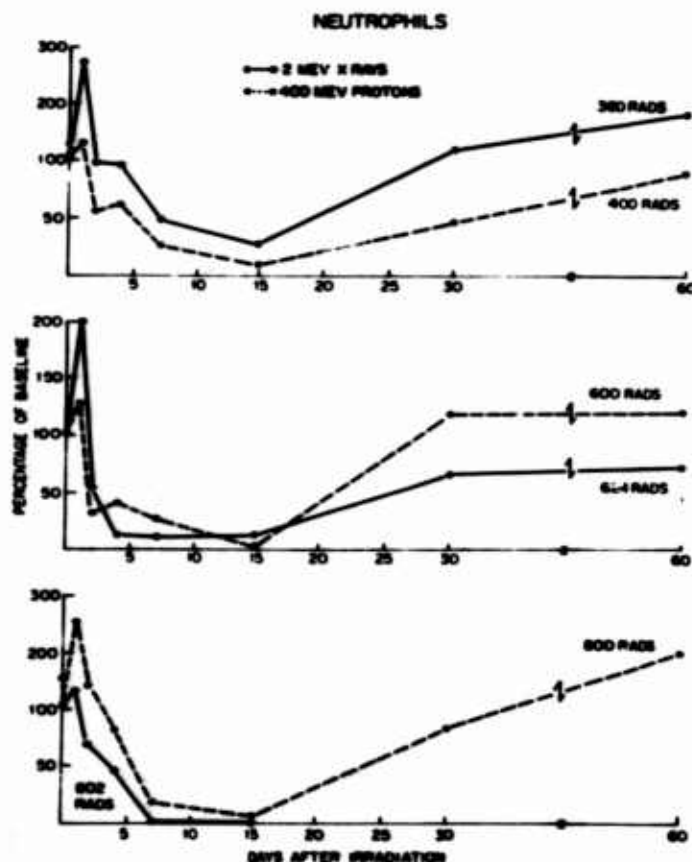


FIGURE 4

Neutrophil counts after 400 Mev protons and 2 Mev x-rays.

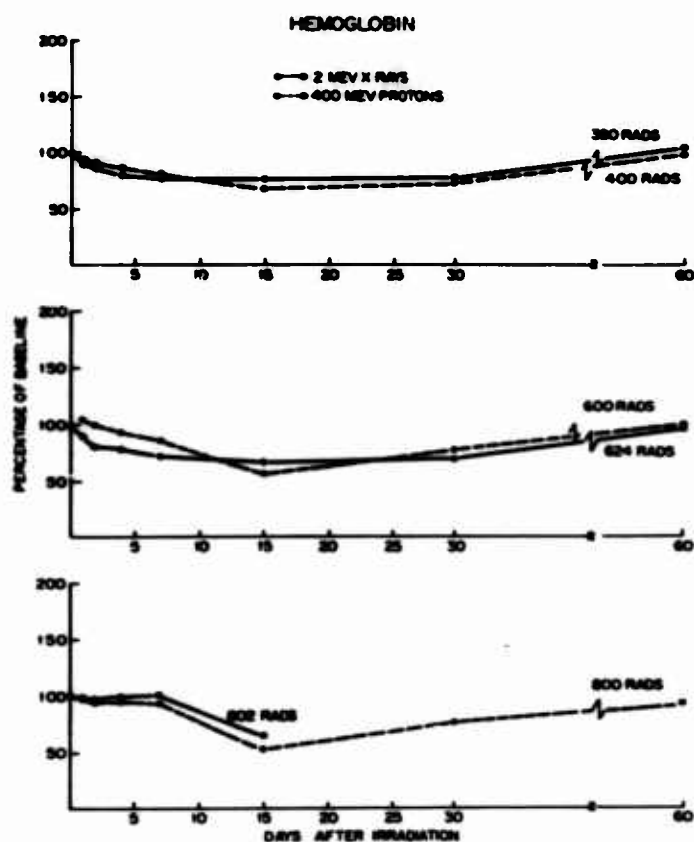


FIGURE 7

Hemoglobin concentrations after 400 Mev protons and 2 Mev x-rays.

alyses, which consider a wide variety of nuclear processes in addition to primary ionization. Therefore, the rad doses based on these data include contributions from both ionization and the nuclear processes. When biologic responses after equivalent doses of 400 Mev protons are compared with effects produced by 2 Mev x-rays, no real differences are found, except for relatively minor differences in clinical courses. This similarity is emphasized by figures 3-8. In these figures the response of the total white

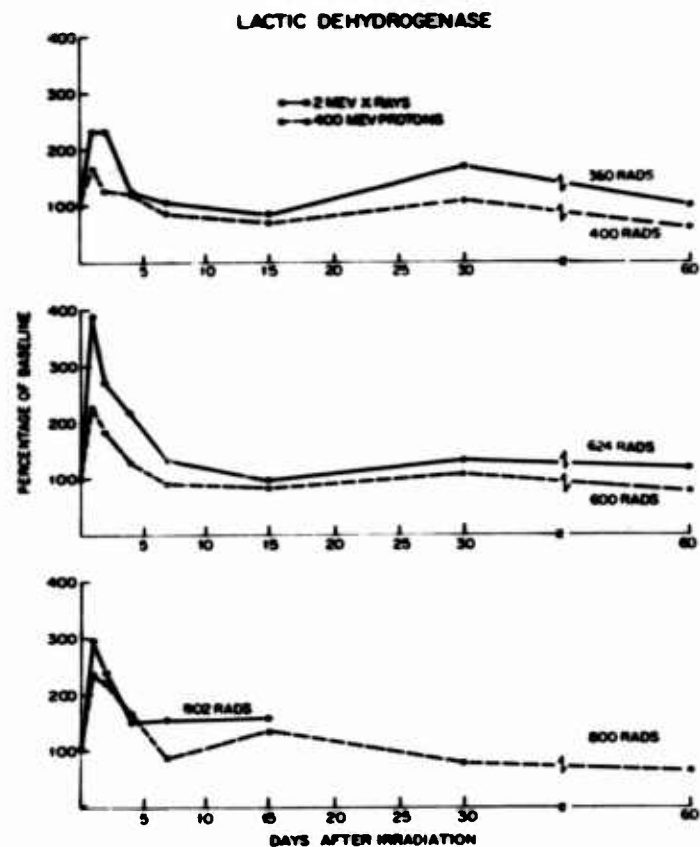


FIGURE 8

Serum lactic dehydrogenase (LDH) concentrations after 400 Mev protons and 2 Mev x-rays.

cell counts, the neutrophil counts, the lymphocyte counts, the platelet counts, the hemoglobin concentration, and the LDH concentrations after 400 Mev protons is compared with results produced by equivalent doses of the 2 Mev x-irradiations. The similarity of responses indicates that the RBE is unity for changes in these measurements. The ^{59}Fe ferrokinetics given in table IX also emphasize this point. Therefore, we have no evidence to suggest that the response to 400 Mev protons differs significantly from the response to 2 Mev x-rays.

REFERENCES

1. Dalrymple, G. V., I. R. Lindsay, J. J. Ghidoni, H. L. Kundel, E. T. Still, R. Jacobs, G. H. Williams, J. D. Hall, and I. L. Morgan. Some effects of whole-body 32 Mev proton irradiation on primates. The radiations of space II. SAM-TR-65-43, June 1965.
2. Lindsay, I. R., G. V. Dalrymple, J. J. Ghidoni, J. C. Mitchell, and I. L. Morgan. Some effects of whole body 55 Mev proton irradiations on primates. Radiat. Res. (Submitted for publication)

3. Dalrymple, G. V., I. R. Lindsay, J. J. Ghidoni, J. C. Mitchell, and H. L. Kundel. Some effects of 138 Mev protons on primates. The radiations of space III. SAM-TR-65-58 (In press).
4. Turner, J. E., C. D. Zerby, R. L. Woodyard, H. A. Wright, W. E. Kinney, W. S. Snyder, and J. Neufeld. Calculation of radiation dose from protons to 400 Mev. *Health Phys.* 10:783-808 (1964).
5. Solar proton manual. In McDonald, F. B. (ed.). NASA Technical Report NASA TR, R-169 (1963).
6. Dalrymple, G. V., I. R. Lindsay, and J. J. Ghidoni. The effect of 2 Mev whole body x-irradiation on primates. *Radiat. Res.* 25:377-400 (1965).
7. Mitchell, J. C., G. V. Dalrymple, G. H. Williams, J. D. Hall, and I. L. Morgan. Proton depth dose dosimetry. *Radiat. Res.* (Submitted for publication)
8. Williams, G. H., J. D. Hall, and I. L. Morgan. Irradiation of primates with protons. *Radiat. Res.* (Submitted for publication)
9. Lajtha, L. G. The use of isotopes in haematology. Springfield, Ill.: Charles C Thomas, 1961.
10. Finney, J. D. Probit analysis. Cambridge, Eng.: Cambridge University Press, 1952.
11. Haigh, M. V., and E. Paterson. Effects of a single session of whole body irradiation in the rhesus monkey. *Brit. J. Radiol.* 29:148-157 (1956).
12. Eldred, E., and W. V. Trowbridge. Radiation sickness in the monkey. *Radiology* 62:63-73 (1954).
13. Allen, R. G., F. A. Brown, L. C. Logie, D. R. Rovner, S. G. Wilson, and R. W. Zellmer. Acute effects of gamma radiation in primates. *Radiat. Res.* 12:532-559 (1960).
14. Vogel, H. H., J. W. Clark, and D. L. Jordan. Comparative mortality after 24-hour whole-body exposures of mice to fission neutrons and cobalt 60 gamma rays. *Radiat. Res.* 6:460-468 (1957).
15. Neal, F. E. Variation of acute mortality with dose rate in mice exposed to single large doses of whole body x-radiation. *Int. J. Radiat. Biol.* 2:295-300 (1960).
16. Bateman, J. L., V. P. Bond, and J. S. Robertson. Dose rate dependence of early radiation effects in small mammals. *Radiology* 79:1008-1014 (1962).
17. Dalrymple, G. V., I. R. Lindsay, J. D. Hall, J. C. Mitchell, J. J. Ghidoni, H. L. Kundel, and I. L. Morgan. An investigation of the relative biologic effectiveness of 138 Mev protons as compared to Co⁶⁰ gamma radiation. SAM-TR-65-52, Aug. 1965.
18. Sondhaus, C. A., J. K. Ashikawa, C. A. Tobias, and V. Paschkes. Some factors influencing RBE of high energy protons. Univ. of California, Lawrence Radiation Laboratory Report UCRL-10683:12-13 (1962).
19. Ashikawa, J. K., C. A. Sondhaus, C. A. Tobias, and D. Love. Difference in acute radiation syndrome and its dose dependence for 100 kVp x-rays and 730 Mev protons. Univ. of California, Lawrence Radiation Laboratory Report UCRL-10683:10-11 (1962).
20. Stefanini, M., and W. Dameshek. The hemorrhagic disorders, a clinical and therapeutic approach. New York: Grune and Stratton, 1955.
21. Freeman, G. Second Conference on Folic Acid, antagonists in the treatment of leukemia. *Blood* 7:153-156 (1952).
22. Freeman, G. The anticoagulant effect of bacterial polysaccharides in normal and thrombocytopenia plasma of leukemia. *Blood* 7:235-242 (1952).
23. Freeman, G., and E. S. Buckley. Serum polysaccharide and fever in thrombocytopenic bleeding of leukemia. *Blood* 9:586-594 (1954).

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